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*APPLICATION NUMBER:*

**22-233**

**CHEMISTRY REVIEW(S)**

# **NDA 22-233**

**Aloxi (Palonosetron HCl) Capsules, 0.5 mg**

**Helsinn Healthcare SA**

**Zhengfang Ge, Ph.D.**

**Branch III, Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment**

**For**

**DIVISION OF GASTROINTESTINAL AND COAGULATION  
DRUG PRODUCTS**

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# Chemistry Review Data Sheet

1. **NDA 22-233**

2. **REVIEW #:** 1

3. **REVIEW DATE:** Aug 13, 2008

4. **REVIEWER:** Zhengfang Ge, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents

Document Date

None

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed

Document Date

Original

Oct. 24, 2007

Amendment

Jan. 4, 2008

Amendment

Apr. 18, 2008

Amendment

Aug. 8, 2008

7. **NAME & ADDRESS OF APPLICANT:**

Name: Helsinn Healthcare SA

Address: Via Pian Scairolo  
6912 Pazzallo (Lugano)  
Switzerland

Representative: Craig Lehmann, Pharm.D.  
August Consulting Inc

Telephone: (512) 347-1755

Fax: (512) 347-9375

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) **Proprietary Name:** (3a $\underline{S}$ )-2-[( $\underline{S}$ )-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1 $\underline{H}$ -benz[ $\underline{de}$ ]isoquinoline hydrochloride

b) **Non-Proprietary Name (USAN):** palonosetron hydrochloride

c) **Code Name/# (ONDQA only):** NA

d) **Chem. Type/Submission Priority (ONDQA only):**

- **Chem. Type:** 5

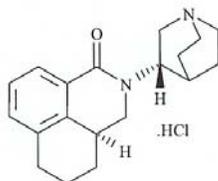
## Chemistry Review Data Sheet

- **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(1)
10. **PHARMACOL. CATEGORY:** antiemetic and antinauseant
11. **DOSAGE FORM:** Capsules
12. **STRENGTH/POTENCY:** 0.50mg
13. **ROUTE OF ADMINISTRATION:** oral
14. **Rx/OTC DISPENSED:**  Rx  OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

**CHEMICAL NAME:** (3a*S*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride



**MOLECULAR FORMULA:** C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O.HCl  
**MOLECULAR WEIGHT:** 332.87

17. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
16063	II	Helsinn Advanced Synthesis	Drug substance (b) (4)	1	Adequate	June 2, 2008	
				1	Adequate	June 2, 2008	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Review	NDA 21,732	By M. Kowblansky

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	Aug 13, 2008	Office of Compliance
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMETS	See section II/A	Aug 1, 2008	Richard Abate
EA	Adequate		Section II/B of this review
Microbiology	NA		

\*The applicant appropriately claims categorical exclusion on the basis that the concentration of the active moiety will not exceed 1 ppb at the point of entry into the aquatic environment.

# The Chemistry Review for NDA 22-233

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The sponsor has provided adequate information in the original submission and subsequent amendments to assure identity, strength, purity, and the quality of the drug product. Therefore, from a CMC point of view, this NDA can be approved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance

The active drug substance is palonosetron hydrochloride manufactured by Helsinn Healthcare, the same manufacturer as for the previously approved palonosetron injectable drug product (NDA 21-732). The sponsor cross-referenced DMF 16063 for complete CMC information. The DMF was reviewed by Dr. Kowblansky for NDA 21-732. Amendments then after were reviewed for this NDA separately and were found satisfactory to support the approval of this NDA.

##### Drug Product

The palonosetron soft gel capsules are prepared in 0.5 mg strength and are packaged in 30 cc white HDPE bottles (5 capsules per bottle) with child resistant closures. All inactive components are compendial with the exception of mono- and di-glycerides of Capryl/Capric acid (b) (4) and polyglyceryl oleate (b) (4) for which specifications are provided in the submission. The proposed commercial formulation differs from the formulation used in Phase 1, 2, and 3 clinical studies. The level of (b) (4) was reduced from (b) (4) and (b) (4) was increased from (b) (4) (u) (+) (b) (4). However, the reduction in (b) (4) has no impact on the bioavailability as evidenced by bioequivalence studies that showed the two formulations to be bioequivalent. The commercial drug products are manufactured at Catalent Pharma (Somerset, NJ), the same manufacturing site

**Helsinn Healthcare SA: Palonosetron  
NDA 22-233**

where capsules used in clinical studies were prepared. The sponsor cross referenced [REDACTED] (b) (4)

[REDACTED] The related information in the DMF was reviewed separately and was found adequate to support this NDA.

The specification for palonosetron HCl capsules includes common testing for immediate release oral dosage drug products. It includes testing for appearance, identification (HPLC and UV), assay, impurities, content uniformity, dissolution, BHA content and microbial tests. Specification is reviewed and found adequate to control the identity, strength, purity and quality of the drug product.

In the original NDA submission and subsequent amendments, the sponsor provided 18 months and 6 months stability data under controlled room condition and accelerate condition, respectively, for three registration batches of the drug products, and 24 months supportive stability data for one batch of the drug products with the old formulation. The sponsor also provided 12 months stability data for three registration batch drug products in bulk package. The stability results are within the acceptance criteria, even the batch with the old formulation meets the specification after 24 months storage. The sponsor proposed an expiration of 30 months based on the stability data. The sponsor's proposal of expiration date is acceptable based on the stability results.

Aloxi (palonosetron HCl) was proposed as the product name. According to the current labeling practices for the product name and strengths, the strength should be expressed in terms of the established name, which would be 0.56 mg of palonosetron HCl for this product. However, the sponsor proposed to use 0.5 mg which is the strength of palonosetron free base. The sponsor's labeling proposal using palonosetron HCl 0.5 mg with a sub note indicating each capsule contains 0.5 mg palonosetron free base as 0.56 mg palonosetron HCl is acceptable in order to be consistent with the labeling for the approved Aloxi products.

The sponsor appropriately claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of palonosetron at the point of entry into the aquatic environment will be below 1 part per billion (the estimated concentration is 0.068 ppb).

**B. Description of How the Drug Product is Intended to be Used**

Dosage for Adults - one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy.

**Helsinn Healthcare SA: Palonosetron  
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**C. Basis for Approvability or Not-Approval Recommendation**

The information provided in the NDA submission as summarised in previous section is adequate to support the identity, strength, purity and quality for the 0.5 mg drug product. Satisfactory recommendation from facility inspections in the manufacture of the drug substance and drug product was made by the Office of Compliance on 13-Aug-2008. Therefore, the NDA can be approved from the CMC perspective.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemistry Reviewer: Zhengfang Ge, Ph.D.  
Branch Chief: Moo Jhong Rhee, Ph.D.  
PAL: Marie Kowblanski, Ph.D.  
Project Manager: Jagjit Grewal

**B. CC Block**

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Moo-Jhong Rhee  
8/14/2008 01:09:02 PM  
CHEMIST  
Chief, Branch III

Initial Quality Assessment  
Branch 3  
Pre-Marketing Assessment Division 2

**OND Division:** Division of Gastroenterology Products  
**NDA:** 22-233  
**Applicant:** Helsinn Healthcare  
**Stamp Date:** 10/25/2007  
**Received by PAL:** 10/30/2007  
**Review Date:** 11/30/2007  
**PDUFA Date:** 8/30/08/2008  
**Filing Meeting:** 11/30/07  
**Proposed Trademark:** ALOXI® (palonosetron hydrochloride) Capsules  
**Established Name:** Palonosetron hydrochloride  
**Dosage Form:** capsules  
**Route of Administration:** oral  
**Indication:** Prevention of nausea and vomiting associated with chemotherapy

**P.A.L.:** Marie Kowblansky, PhD

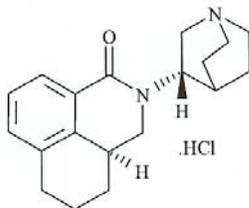
	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

### A. Summary

ALOXI® (palonosetron hydrochloride) Capsules, is intended for the prevention of acute nausea and vomiting in patients receiving moderately or highly emetogenic cancer chemotherapy. The proposed product is a softgel containing 0.5 mg of palonosetron (as palonosetron hydrochloride) in a liquid formulation, with a recommendation to administer one capsule approximately one hour prior to initiating chemotherapy. This product, which was studied under IND 42,886, is being filed by Helsinn Healthcare as a 505(b)(1) application. The same firm is the holder of NDA 21-372, an approved injectable formulation of palonosetron hydrochloride, also marketed under the ALOXI® name. Since this is a new formulation of a currently approved drug, this is classified as a Type 3 application in the Chemical Classification Code.

### Drug Substance

The active drug substance, which will be manufactured by Helsinn Healthcare, is palonosetron hydrochloride



Only limited chemistry, manufacturing, and controls information regarding this drug substance is provided in the submission; reference is made to Helsinn's DMF 16,063 for complete CMC

information. The above structure indicates that palonosetron contains two chiral centers, making four stereoisomers of the molecule possible. The molecule is synthesised, however, as the (S, S) stereoisomer. Palonosetron hydrochloride is freely soluble in water and propylene glycol and only slightly soluble in ethanol, (b) (4). It is classified as a Class 1 drug substance in the Biopharmaceutics Classification System. Two polymorphic forms, in addition to an amorphous form, have been identified. However, because the drug product is a solution-filled capsule, neither polymorphic form nor particle size is critical to the formulation.

The specification for palonosetron hydrochloride drug substance is the same as approved for use in NDA 21-372, ALOXI® (palonosetron HCl) for Injection (0.25 mg/5 mL per vial). It includes testing for identity (IR, UV), optical rotation, clarity of solution, pH, loss on drying, residue on ignition, heavy metals, chloride content, assay, related substances, residual solvents, bioburden, and endotoxins. For unidentified impurities, no individual impurity will exceed 0.1%, in accord with ICH guidance. For the two specified impurities (b) (4) (b) (4) which are respectively the (b) (4) (b) (4) (b) (4) the limits have been set at (b) (4) % for each. From toxicological studies conducted in conjunction with NDA 21-372 it was concluded that the (b) (4) % limits were well within the margin of safety and were found acceptable. (See memorandum to NDA 21-372 from Y. Chopra dated 7/10/2003, where (b) (4) (b) (4) are respectively identified as (b) (4) (b) (4). For the product currently under consideration, where the daily dose is 0.5 mg, the proposed limits are also well within the safety limits.

**Drug Product**

The palonosetron capsules will be prepared in only one strength, 0.50 mg palonosetron per capsule, and contain the following liquid formulation that will be filled into capsules

Ingredient	Use	% w/w	Amount (mg/Capsule)			
Palonosetron HCl	Active ingredient	0.42	0.56 <sup>7</sup>			
Mono- and di-glycerides of Capryl/Capric acid, (b) (4) (b) (4)						
Glycerin, (b) (4) USP/Ph Eur						
Polyglyceryl oleate, (b) (4) (b) (4)						
Purified water, USP/Ph Eur						
Butylated hydroxyanisole (BHA), NF/Ph Eur (b) (4)						
<b>Theoretical Fill Weight</b>					100%	133.00 mg

<sup>1</sup> Generally recognized as safe (GRAS) according to 21 CFR 184.1505, DMF (b) (4)

<sup>2</sup> Classified as food grade (USFA, FCC)

<sup>7</sup> Corresponds to 0.50 mg free base

All inactive components are compendial with the exception of mono- and di-glycerides of Capryl/Capric acid (b) (4) and polyglyceryl oleate (b) (4) for which specifications are provided in the submission. Data are provided to show that the excipients, including non-compendial ones are all well below the maximum levels reported in the FDA inactive ingredients base for marketed oral products.

The proposed commercial formulation differs from the formulation used in Phase 1, 2, and 3 clinical studies. The level of (b) (4) was reduced from (b) (4) and (b) (4) was increased from (b) (4) (b) (4) (b) (4)

(b) (4) (b) (4) However, the reduction in (b) (4) has no impact on the bioavailability as evidenced by bioequivalence studies that showed the two formulations to be bioequivalent.

The above formulation is encapsulated in 3-oval softgel capsule shells imprinted with (b) (4) black ink. (b) (4)

The commercial drug product will be manufactured at Catalent Pharma (Somerset, NJ), the same manufacturing site where capsules used in clinical studies were prepared. A process flow diagram describing the manufacturing process is provided in the submission and reference is made to (b) (4) describing the composition and manufacture of the softgel capsules.

The capsules will be packaged in 30cc white, high density polyethylene (HDPE) bottles (5 capsules per bottle), with child-resistant closures. Secondary packaging (carton) is used to minimize the formation of impurity (b) (4)

The product will conform to the following specifications:

Test	Specification	R <sup>1</sup>	S <sup>1</sup>	Helsinn Method Number
Appearance	Light beige opaque oval softgels printed with logo "AIO" in black ink			(b) (4)
Aspect of the content (Fill appearance)	(b) (4)			
Identification by HPLC				
Identification by UV				
Assay (Content of Palonosetron)				
Specified Impurities:	(b) (4)			
Unspecified Impurities:				
Total Unspecified Impurities				
Total Impurities, (Specified and Unspecified)				
Content Uniformity				
Dissolution				
BHA Content				
Total aerobic microbial count				
Total combined mold & yeast count				
<i>Escherichia coli</i>				
<i>Salmonella species</i>				
<i>Staphylococcus aureus</i>				
<i>Pseudomonas aeruginosa</i>				

1 – R = test performed for final product release; S = test performed for stability

Impurity (b) (4) is the primary degradation product, but it is also the primary metabolite. Consequently the proposed (b) (4) specification limit is acceptable.

The applicant proposes a (b) (4) expiration for the product. To support this request, (b) (4) of 25°C stability data and (b) (4) of accelerated stability data are provided for three batches of the proposed commercial product, with (b) (4) of supporting data for one batch of the less stable formulation used in clinical trials. The data show that the reformulated product is indeed more stable than the original formulation. Even so, the less stable formulation showed the palonosetron content to be 97% after (b) (4) at 25°C and 96% after (b) (4) at 40°C. Thus it may be acceptable to use stability data from the original formulation to support a (b) (4) expiry.

Helsinn Healthcare appropriately claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of palonosetron at the point of entry into the aquatic environment will be below 1 part per billion (the estimated concentration is 0.068 ppb).

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

## ***B. Critical issues for review***

The applicant has previous experience with this drug substance and consequently has submitted a lucid application, with no major deficiencies being identified from this initial overview. Based on this initial assessment, three issues will need to be more closely scrutinized:

- A determination will need to be made whether the specifications for the non-compendial excipients provide adequate control to ensure acceptable product performance and safety.
- The dissolution acceptance criterion requires that not less than (b) (4) of the drug substance be dissolved in (b) (4). This requirement may be too liberal in that all batch data show that (b) (4). The appropriateness of this specification should be evaluated based on the full dissolution profiles.
- The stability data should be closely scrutinized to determine if a (b) (4) is warranted.

## ***C. Comments for 74-Day Letter -- None***

Marie Kowblansky, PhD  
Pharmaceutical Assessment Lead

11/30/2007  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

11/30/2007  
Date

Manufacturing Sites

**Establishment Information:**

Establishment	Establishment Number	Contact	Function
Helsinn Advanced Synthesis SA Via Industria 24 6710 Biasca Switzerland	3002807151	Dr. Paolo Guainazzi, General Manager Telephone: +41 91 873 0113 Fax: +41 91 873 0110	Manufacturing, packaging and testing of drug substance
(b) (4)			
Catalent Pharma Solutions (formerly Cardinal Health, Inc.) 14 Schoolhouse Road Somerset, New Jersey 08873 USA	2249948	Dee Abelha, Director of Quality Assurance Telephone: 732-537-6148 Fax: 732-537-6466	Manufacturing, and release and stability testing of drug product
(b) (4)			
Catalent Pharma Solutions (formerly Cardinal Health PTS, LLC) 3001 Red Lion Road Philadelphia, Pennsylvania 19114 USA	Labeler Code: 055154	Gregory Lane, Senior Director of Quality Assurance Telephone: 215-613-3178 Fax: 215-613-3000	Primary packager and labeler of drug product
Helsinn Birex Pharmaceuticals Ltd. (HPB) Damastown Mulhuddart-Dublin 15 Ireland	3003724414	Margaret Bolton, Director Quality Assurance Telephone: 011-35-31-8089630	Alternate labeler, secondary packager, performs release to market of drug product

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/s/

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Chief, Branch III